

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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|---|---|
| In re Application of: Ashkenazi et al.                                  | Group Art Unit: 1647  |
| Serial No.: 09/903,925  | Examiner: Fozia Hamid   |
| Filed: July 11, 2001  | <b>CERTIFICATE OF MAILING</b><br>I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on |
| For: SECRETED AND<br>TRANSMEMBRANE<br>POLYPEPTIDES AND NUCLEIC<br>ACIDS | Date  |

DECLARATION OF AUDREY D. GODDARD, Ph.D UNDER 37 C.F.R. § 1.132

Assistant Commissioner of Patents  
Washington, D.C. 20231

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Sir:

I, Audrey D. Goddard, Ph.D. do hereby declare and say as follows:

1. I am a Senior Clinical Scientist at the Experimental Medicine/BioOncology, Medical Affairs Department of Genentech, Inc., South San Francisco, California 94080.
2. Between 1993 and 2001, I headed the DNA Sequencing Laboratory at the Molecular Biology Department of Genentech, Inc. During this time, my responsibilities included the identification and characterization of genes contributing to the oncogenic process, and determination of the chromosomal localization of novel genes.
3. My scientific Curriculum Vitae, including my list of publications, is attached to and forms part of this Declaration (Exhibit A).

Serial No.: \*

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4. I am familiar with a variety of techniques known in the art for detecting and quantifying the amplification of oncogenes in cancer, including the quantitative TaqMan PCR (i.e., "gene amplification") assay described in the above captioned patent application.

5. The TaqMan PCR assay is described, for example, in the following scientific publications: Higuchi *et al.*, Biotechnology 10:413-417 (1992) (Exhibit B); Livak *et al.*, PCR Methods Appl., 4:357-362 (1995) (Exhibit C) and Heid *et al.*, Genome Res. 6:986-994 (1996) (Exhibit D). Briefly, the assay is based on the principle that successful PCR yields a fluorescent signal due to Taq DNA polymerase-mediated exonuclease digestion of a fluorescently labeled oligonucleotide that is homologous to a sequence between two PCR primers. The extent of digestion depends directly on the amount of PCR, and can be quantified accurately by measuring the increment in fluorescence that results from decreased energy transfer. This is an extremely sensitive technique, which allows detection in the exponential phase of the PCR reaction and, as a result, leads to accurate determination of gene copy number.

6. The quantitative fluorescent TaqMan PCR assay has been extensively and successfully used to characterize genes involved in cancer development and progression. Amplification of protooncogenes has been studied in a variety of human tumors, and is widely considered as having etiological, diagnostic and prognostic significance. This use of the quantitative TaqMan PCR assay is exemplified by the following scientific publications: Pennica *et al.*, Proc. Natl. Acad. Sci. USA 95(25):14717-14722 (1998) (Exhibit E); Pitti *et al.*, Nature 396(6712):699-703 (1998) (Exhibit F) and Bieche *et al.*, Int. J. Cancer 78:661-666 (1998) (Exhibit G), the first two of which I am co-author. In particular, Pennica *et al.* have used the quantitative TaqMan PCR assay to study relative gene amplification of WISP and c-myc in various cell lines, colorectal tumors and normal mucosa. Pitti *et al.* studied the genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer, using the quantitative TaqMan PCR assay. Bieche *et al.* used the assay to study gene amplification in breast cancer.

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7. It is my personal experience that the quantitative TaqMan PCR technique is technically sensitive enough to detect at least a 2-fold increase in gene copy number relative to control. It is further my considered scientific opinion that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

8. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Jan. 16, 2003

Date

Audrey D. Goddard

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## PROFESSIONAL EXPERIENCE

Genentech, Inc.

1993-present

South San Francisco, CA

**2001 - present      Senior Clinical Scientist**

Experimental Medicine / BioOncology, Medical Affairs

Responsibilities:

- *Companion diagnostic oncology products*
- *Acquisition of clinical samples from Genentech's clinical trials for translational research*
- *Translational research using clinical specimen and data for drug development and diagnostics*
- *Member of Development Science Review Committee, Diagnostic Oversight Team, 21 CFR Part 11 Subteam*

Interests:

- *Ethical and legal implications of experiments with clinical specimens and data*
- *Application of pharmacogenomics in clinical trials*

**1998 - 2001      Senior Scientist**

Head of the DNA Sequencing Laboratory, Molecular Biology Department, Research

Responsibilities:

- *Management of a laboratory of up to nineteen –including postdoctoral fellow, associate scientist, senior research associate and research assistants/associate levels*
- *Management of a \$750K budget*
- *DNA sequencing core facility supporting a 350+ person research facility.*
- *DNA sequencing for high throughput gene discovery, - ESTs, cDNAs, and constructs*
- *Genomic sequence analysis and gene identification*
- *DNA sequence and primary protein analysis*

Research:

- *Chromosomal localization of novel genes*
- *Identification and characterization of genes contributing to the oncogenic process*
- *Identification and characterization of genes contributing to inflammatory diseases*
- *Design and development of schemes for high throughput genomic DNA sequence analysis*
- *Candidate gene prediction and evaluation*

**1993 - 1998      Scientist**

Head of the DNA Sequencing Laboratory, Molecular Biology Department, Research

**Responsibilities**

- *DNA sequencing core facility supporting a 350+ person research facility*
- *Assumed responsibility for a pre-existing team of five technicians and expanded the group into fifteen, introducing a level of middle management and additional areas of research*
- *Participated in the development of the basic plan for high throughput secreted protein discovery program – sequencing strategies, data analysis and tracking, database design*
- *High throughput EST and cDNA sequencing for new gene identification.*
- *Design and implementation of analysis tools required for high throughput gene identification.*
- *Chromosomal localization of genes encoding novel secreted proteins.*

**Research:**

- *Genomic sequence scanning for new gene discovery.*
- *Development of signal peptide selection methods.*
- *Evaluation of candidate disease genes.*
- *Growth hormone receptor gene SNPs in children with Idiopathic short stature*

**Imperial Cancer Research Fund  
London, UK with Dr. Ellen Solomon**

**1989-1992**

**6/89 –12/92 Postdoctoral Fellow**

- *Cloning and characterization of the genes fused at the acute promyelocytic leukemia translocation breakpoints on chromosomes 17 and 15.*
- *Prepared a successfully funded European Union multi-center grant application*

**McMaster University  
Hamilton, Ontario, Canada with Dr. G. D. Sweeney**

**1983**

**5/83 – 8/83: NSERC Summer Student**

- *In vitro metabolism of  $\beta$ -naphthoflavone in C57BL/6J and DBA mice*

**EDUCATION**

**Ph.D.**

"Phenotypic and genotypic effects of mutations in the human retinoblastoma gene."

**Supervisor:** Dr. R. A. Phillips

University of Toronto  
Toronto, Ontario, Canada.  
Department of Medical  
Biophysics.

1989

**Honours B.Sc**

"The *in vitro* metabolism of the cytochrome P-448 inducer  $\beta$ -naphthoflavone in C57BL/6J mice."

**Supervisor:** Dr. G. D. Sweeney

McMaster University,  
Hamilton, Ontario, Canada.  
Department of Biochemistry

1983

## ACADEMIC AWARDS

|   |           |
|---|-----------|
| Imperial Cancer Research Fund Postdoctoral Fellowship     | 1989-1992 |
| Medical Research Council Studentship                      | 1983-1988 |
| NSERC Undergraduate Summer Research Award                 | 1983      |
| Society of Chemical Industry Merit Award (Hons. Biochem.) | 1983      |
| Dr. Harry Lyman Hooker Scholarship                        | 1981-1983 |
| J.L.W. Gill Scholarship                                   | 1981-1982 |
| Business and Professional Women's Club Scholarship        | 1980-1981 |
| Wyerhauser Foundation Scholarship                         | 1979-1980 |

## INVITED PRESENTATIONS

Genentech's gene discovery pipeline: High throughput identification, cloning and characterization of novel genes. Functional Genomics: From Genome to Function, Litchfield Park, AZ, USA. October 2000

High throughput identification, cloning and characterization of novel genes. G2K:Back to Science, Advances in Genome Biology and Technology I. Marco Island, FL, USA. February 2000

Quality control in DNA Sequencing: The use of Phred and Phrap. Bay Area Sequencing Users Meeting, Berkeley, CA, USA. April 1999

High throughput secreted protein identification and cloning. Tenth International Genome Sequencing and Analysis Conference, Miami, FL, USA. September 1998

The evolution of DNA sequencing: The Genentech perspective. Bay Area Sequencing Users Meeting, Berkeley, CA, USA. May 1998

Partial Growth Hormone Insensitivity: The role of GH-receptor mutations in Idiopathic Short Stature. Tenth Annual National Cooperative Growth Study Investigators Meeting, San Francisco, CA, USA. October, 1996

Growth hormone (GH) receptor defects are present in selected children with non-GH-deficient short stature: A molecular basis for partial GH-insensitivity. 76<sup>th</sup> Annual Meeting of The Endocrine Society, Anaheim, CA, USA. June 1994

A previously uncharacterized gene, myl, is fused to the retinoic acid receptor alpha gene in acute promyelocytic leukemia. XV International Association for Comparative Research on Leukemia and Related Disease, Padua, Italy. October 1991

## PATENTS

Goddard A, Godowski PJ, Gurney AL. NL2 Tie ligand homologue polypeptide. Patent Number: 6,455,496. Date of Patent: Sept. 24, 2002.

**Goddard A**, Godowski PJ and Gurney AL. NL3 Tie ligand homologue nucleic acids. Patent Number: 6,426,218. Date of Patent: July 30, 2002.

Godowski P, Gurney A, Hillan KJ, Botstein D, **Goddard A**, Roy M, Ferrara N, Tumas D, Schwall R. NL4 Tie ligand homologue nucleic acid. Patent Number: 6,413,770. Date of Patent: July 2, 2002.

Ashkenazi A, Fong S, **Goddard A**, Gurney AL, Napier MA, Tumas D, Wood WI. Nucleic acid encoding A-33 related antigen poly peptides. Patent Number: 6,410,708. Date of Patent: Jun. 25, 2002.

Botstein DA, Cohen RL, **Goddard AD**, Gurney AL, Hillan KJ, Lawrence DA, Levine AJ, Pennica D, Roy MA and Wood WI. WISP polypeptides and nucleic acids encoding same. Patent Number: 6,387,657. Date of Patent: May 14, 2002.

**Goddard A**, Godowski PJ and Gurney AL. Tie ligands. Patent Number: 6,372,491. Date of Patent: April 16, 2002.

Godowski PJ, Gurney AL, **Goddard A** and Hillan K. TIE ligand homologue antibody. Patent Number: 6,350,450. Date of Patent: Feb. 26, 2002.

Fong S, Ferrara N, **Goddard A**, Godowski PJ, Gurney AL, Hillan K and Williams PM. Tie receptor tyrosine kinase ligand homologues. Patent Number: 6,348,351. Date of Patent: Feb. 19, 2002.

**Goddard A**, Godowski PJ and Gurney AL. Ligand homologues. Patent Number: 6,348,350. Date of Patent: Feb. 19, 2002.

Attie KM, Carlsson LMS, Gesundheit N and **Goddard A**. Treatment of partial growth hormone insensitivity syndrome. Patent Number: 6,207,640. Date of Patent: March 27, 2001.

Fong S, Ferrara N, **Goddard A**, Godowski PJ, Gurney AL, Hillan K and Williams PM. Nucleic acids encoding NL-3. Patent Number: 6,074,873. Date of Patent: June 13, 2000

Attie K, Carlsson LMS, Gesundheit N and **Goddard A**. Treatment of partial growth hormone insensitivity syndrome. Patent Number: 5,824,642. Date of Patent: October 20, 1998

Attie K, Carlsson LMS, Gesundheit N and **Goddard A**. Treatment of partial growth hormone insensitivity syndrome. Patent Number: 5,646,113. Date of Patent: July 8, 1997

Multiple additional provisional applications filed

## PUBLICATIONS

- Seshasayee D, Dowd P, Gu Q, Erickson S, **Goddard AD**. Comparative sequence analysis of the *HER2* locus in mouse and man. Manuscript in preparation.
- Abuzzahab MJ, **Goddard A**, Grigorescu F, Lautier C, Smith RJ and Chernausek SD. Human IGF-1 receptor mutations resulting in pre- and post-natal growth retardation. Manuscript in preparation.
- Aggarwal S, Xie, M-H, Foster J, Frantz G, Stinson J, Corpuz RT, Simmons L, Hillan K, Yansura DG, Vandlen RL, **Goddard AD** and Gurney AL. FHFR, a novel receptor for the fibroblast growth factors. Manuscript submitted.
- Adams SH, Chui C, Schilbach SL, Yu XX, **Goddard AD**, Grimaldi JC, Lee J, Dowd P, Colman S., Lewin DA. (2001) BFIT, a unique acyl-CoA thioesterase induced in thermogenic brown adipose tissue: Cloning, organization of the human gene, and assessment of a potential link to obesity. *Biochemical Journal* **360**: 135-142.
- Lee J, Ho WH, Maruoka M, Corpuz RT, Baldwin DT, Foster JS, **Goddard AD**, Yansura DG, Vandlen RL, Wood WI, Gurney AL. (2001) IL-17E, a novel proinflammatory ligand for the IL-17 receptor homolog IL-17Rh1. *Journal of Biological Chemistry* **276**(2): 1660-1664.
- Xie M-H, Aggarwal S, Ho W-H, Foster J, Zhang Z, Stinson J, Wood WI, **Goddard AD** and Gurney AL. (2000) Interleukin (IL)-22, a novel human cytokine that signals through the interferon-receptor related proteins CRF2-4 and IL-22R. *Journal of Biological Chemistry* **275**: 31335-31339.
- Weiss GA, Watanabe CK, Zhong A, **Goddard A** and Sidhu SS. (2000) Rapid mapping of protein functional epitopes by combinatorial alanine scanning. *Proc. Natl. Acad. Sci. USA* **97**: 8950-8954.
- Guo S, Yamaguchi Y, Schilbach S, Wada T., Lee J, **Goddard A**, French D, Handa H, Rosenthal A. (2000) A regulator of transcriptional elongation controls vertebrate neuronal development. *Nature* **408**: 366-369.
- Yan M, Wang L-C, Hymowitz SG, Schilbach S, Lee J, **Goddard A**, de Vos AM, Gao WQ, Dixit VM. (2000) Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. *Science* **290**: 523-527.
- Sehl PD, Tai JTN, Hillan KJ, Brown LA, **Goddard A**, Yang R, Jin H and Lowe DG. (2000) Application of cDNA microarrays in determining molecular phenotype in cardiac growth, development, and response to injury. *Circulation* **101**: 1990-1999.
- Guo S, Brush J, Teraoka H, **Goddard A**, Wilson SW, Mullins MC and Rosenthal A. (1999) Development of noradrenergic neurons in the zebrafish hindbrain requires BMP, FGF8, and the homeodomain protein soulless/Phox2A. *Neuron* **24**: 555-566.
- Stone D, Murone, M, Luoh, S, Ye W, Armanini P, Gurney A, Phillips HS, Brush, J, **Goddard A**, de Sauvage FJ and Rosenthal A. (1999) Characterization of the human suppressor of fused; a negative regulator of the zinc-finger transcription factor Gli. *J. Cell Sci.* **112**: 4437-4448.
- Xie M-H, Holcomb I, Deuel B, Dowd P, Huang A, Vagts A, Foster J, Liang J, Brush J, Gu Q, Hillan K, **Goddard A** and Gurney, A.L. (1999) FGF-19, a novel fibroblast growth factor with unique specificity for FGFR4. *Cytokine* **11**: 729-735.

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- Sheridan JP, Marsters SA, Pitti RM, Gurney A., Skubatch M, Baldwin D, Ramakrishnan L, Gray CL, Baker K, Wood WI, **Goddard AD**, Godowski P, and Ashkenazi A. (1997) Control of TRAIL-Induced Apoptosis by a Family of Signaling and Decoy Receptors. *Science* **277** (5327): 818-821.

**Goddard AD**, Dowd P, Chernausek S, Geffner M, Gertner J, Hintz R, Hopwood N, Kaplan S, Plotnick L, Rogol A, Rosenfield R, Saenger P, Mauras N, Hershkopf R, Angulo M and Attie, K. (1997) Partial growth hormone insensitivity: The role of growth hormone receptor mutations in idiopathic short stature. *J. Pediatr.* **131**: S51-55.

Klein RD, Sherman D, Ho WH, Stone D, Bennett GL, Moffat B, Vandlen R, Simmons L, Gu Q, Hongo JA, Devaux B, Poulsen K, Armanini M, Nozaki C, Asai N, **Goddard A**, Phillips H, Henderson CE, Takahashi M and Rosenthal A. (1997) A GPI-linked protein that interacts with Ret to form a candidate neurturin receptor. *Nature*. **387**(6634): 717-21.

Stone DM, Hynes M, Armanini M, Swanson TA, Gu Q, Johnson RL, Scott MP, Pennica D, **Goddard A**, Phillips H, Noll M, Hooper JE, de Sauvage F and Rosenthal A. (1996) The tumour-suppressor gene patched encodes a candidate receptor for Sonic hedgehog. *Nature* **384**(6605): 129-34.

Marsters SA, Sheridan JP, Donahue CJ, Pitti RM, Gray CL, **Goddard AD**, Bauer KD and Ashkenazi A. (1996) Apo-3, a new member of the tumor necrosis factor receptor family, contains a death domain and activates apoptosis and NF-kappa  $\beta$ . *Current Biology* **6**(12): 1669-76.

Rothe M, Xiong J, Shu HB, Williamson K, **Goddard A** and Goeddel DV. (1996) I-TRAF is a novel TRAF-interacting protein that regulates TRAF-mediated signal transduction. *Proc. Natl. Acad. Sci. USA* **93**: 8241-8246.

Yang M, Luoh SM, **Goddard A**, Reilly D, Henzel W and Bass S. (1996) The bglX gene located at 47.8 min on the Escherichia coli chromosome encodes a periplasmic beta-glucosidase. *Microbiology* **142**: 1659-65.

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Treanor JJS, Goodman L, de Sauvage F, Stone DM, Poulson KT, Beck CD, Gray C, Armanini MP, Pollocks RA, Hefti F, Phillips HS, **Goddard A**, Moore MW, Buj-Bello A, Davis AM, Asai N, Takahashi M, Vandlen R, Henderson CE and Rosenthal A. (1996) Characterization of a receptor for GDNF. *Nature* **382**: 80-83.

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Bennett BD, Zeigler FC, Gu Q, Fendly B, **Goddard AD**, Gillett N and Matthews W. (1995) Molecular cloning of a ligand for the EPH-related receptor protein-tyrosine kinase Htk. *Proc. Natl. Acad. Sci. USA* **92**: 1866-1870.

Huang X, Yuang J, **Goddard A**, Foulis A, James RF, Lernmark A, Pujol-Borrell R, Rabinovitch A, Somoza N and Stewart TA. (1995) Interferon expression in the pancreases of patients with type I diabetes. *Diabetes* **44**: 658-664.

**Goddard AD**, Yuan JQ, Fairbairn L, Dexter M, Borrow J, Kozak C and Solomon E. (1995) Cloning of the murine homolog of the leukemia-associated PML gene. *Mammalian Genome* **6**: 732-737.

- Goddard AD**, Covello R, Luoh SM, Clackson T, Attie KM, Gesundheit N, Rundle AC, Wells JA, Carlsson LMTI and The Growth Hormone Insensitivity Study Group. (1995) Mutations of the growth hormone receptor in children with idiopathic short stature. *N. Engl. J. Med.* **333**: 1093-1098.
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- Mark MR, Scadden DT, Wang Z, Gu Q, **Goddard A** and Godowski PJ. (1994) Rse, a novel receptor-type tyrosine kinase with homology to Axl/Ufo, is expressed at high levels in the brain. *Journal of Biological Chemistry* **269**: 10720-10728.
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- Goddard AD**, Borrow J and Solomon E. (1992) A previously uncharacterized gene, PML, is fused to the retinoic acid receptor alpha gene in acute promyelocytic leukemia. *Leukemia* **6 Suppl 3**: 117S-119S.
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